ligand-toxin fusion proteins already exist. The Examiner concludes it would have been obvious to one of ordinary skill in the art to have used the conjugate of Ogata *et al.* as taught by Volk *et al.* and applicant's allegedly admit that conjugates exist to treat pathological immune conditions. The Examiner states that the only factor missing is selection of a ligand that specifically targets receptors on leukocytes, "which should be readily obvious" because:

> once a ligand has been targeted, all that needs to be done would be to conjugate a toxin to said ligand wherein the toxin would inhibit a biological function of the target cell.

This rejection is respectfully traversed.

Relevant law

In order to set forth a prima facie case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 929, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L.

Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. Stratoflex Inc. v Aeroquip Corp., 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 USPQ 1783 (Fed. Cir. 1992).

Also, it is impermissible to ignore the advantages, properties, utilities and unexpected results that flow from the claimed invention; they are part of the invention as a whole. In re Sernaker, 702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983). Unexpected properties must always be considered when determining obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. In re Papesh, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

The claims

The rejected claims

To focus of the remarks herein, the subject matter of the claims, particularly the independent claims is summarized:

Claim 29 is directed to methods of treatment of pathological conditions:

> A method for treating pathological conditions by treating the underlying pathology associated with inflammatory responses and secondary tissue damage associated with activation, proliferation and migration of immune effector cells by inhibiting activation, proliferation or migration of immune effector cells, comprising administering a conjugate to an animal whereby activation, proliferation, migration of the immune effector cells is inhibited wherein:
>
> the conjugate comprises a targeted agent or a portion thereof and a chemokine receptor targeting agent or a portion thereof sufficient to bind to the chemokine receptor and facilitate internalization of the conjugate;

the chemokine receptor targeting agent is a chemokine, an antibody that specifically binds to a chemokine receptor or a fragment of the chemokine or antibody, wherein the chemokine, antibody or fragment thereof binds to the receptor and internalizes the targeted agent in a cell;

the targeted agent or portion thereof, when internalized in a cell, alters metabolism or gene expression in the cell, regulates or alters protein synthesis in the cell, inhibits proliferation of the cell or kills the cell; and

the conjugate binds to a chemokine receptor resulting in internalization of the targeted agent in cells bearing the receptor.

Claim 35 is directed to methods of targeted delivery:

A method of targeted delivery of an agent into cells that express chemokine receptors, comprising associating the agent with a chemokine receptor targeting agent, whereby the agent is internalized by the cells.

Claim 38 is directed to methods of inhibiting proliferation, migration or activation of cells bearing chemokine receptors:

A method of inhibiting proliferation, migration or activation of cells bearing chemokine receptors, comprising contacting the cells with an effective amount of a conjugate that comprises a targeted agent and a chemokine receptor targeting agent, or a portion thereof, wherein the conjugate binds to a chemokine receptor resulting in internalization of the targeted agent in cells bearing the receptor.

Claim 40 is directed to a method for treating secondary tissue damage:

A method for treating secondary tissue damage and associated disease states, comprising administering to a subject in need thereof an effective amount of a therapeutic agent that inhibits the proliferation, migration or physiological activity of secondary tissue damage-promoting inflammatory cells, wherein the therapeutic agent is a conjugate that comprises a chemokine receptor targeting agent and a targeted agent or portion thereof selected so that conjugate binds to a chemokine receptor and internalizes the targeted agent, which inhibits the proliferation, migration or physiological activity of the secondary tissue damage-promoting cells.

Claim 72 is directed to methods of inhibiting proliferation, migration or activation of immune cells:

A method for inhibiting activation, proliferation or migration of immune cells, comprising contacting immune cells with a conjugate that comprises a targeted agent or a portion thereof and a chemokine receptor targeting agent whereby activation, proliferation, migration of the immune cells is inhibited, wherein:

the targeted agent or portion thereof is a toxin;

the chemokine receptor targeting agent is a chemokine or a fragment of thereof that binds to a chemokine receptor and internalizes the targeted agent; and

the conjugate binds to a chemokine receptor resulting in internalization of the targeted agent in cells bearing the receptor.

Claim 86 is directed to methods for developing methods of treatment of inflammatory disorders:

A method of treating a disease or disorder associated with an inflammatory response, comprising:

identifying immune cells that are activated in the disease or disorder;

identifying chemokine receptors expressed on the cells;

preparing a conjugate or plurality thereof containing toxin linked to a chemokine or a plurality of chemokines that specifically bind to the identified chemokine receptors and effect or facilitate internalization of the toxin into the cells; and

contacting the immune cells with the conjugate or plurality thereof.

All claimed methods target conjugates to cells that express chemokine receptors. As described in the application in great detail and summarized in the previous responses, the activation, migration and proliferation of leukocytes are the hallmark of a vast number of immunomodulatory diseases. These cells are responsible for the production of inflammatory mediators and toxic molecules (such as cytokines, reactive oxygen species, metalloproteinases and cytotoxins) that are essential for the host immune defense against invading pathogens, such as bacteria and viruses. Inappropriate triggering, disregulation or over-activation of the immune response is responsible for the damage to normal host tissue witnessed in leukocyte-mediated diseases such as arthritis, multiple sclerosis, and pulmonary diseases. Leukocyte-mediated diseases also include trauma (e.g. spinal cord injury) and cancers and others. In the latter, leukocytes exert tumorigenic effects by nourishing the cancer directly or indirectly (by directing

angiogenesis), by supplying chemokines and growth factors, and aiding metastasis by supplying various extracellular proteases.

Thus leukocytes are the mediators of diseases that can have combinations of allergic, autoimmune, angiogenic, inflammatory, and tumorigenic components. It must be noted that leukocytes are not necessarily the trigger of disease (which may be viral , bacterial, allergen, aberrant gene expression, trauma etc – initiated) but the excess immune (leukocyte) response is responsible for disease manifestation and progression.

This application provides an avenue of the therapeutic intervention that exploits this common underlying response (termed an underlying pathological response in the claims). Selection of this pathway for therapeutic intervention is not new (see discussion below); what is new in this application is the mode of intervention. The instant application provides conjugates that are targeted to specific chemokine receptors. (see, *e.g.*, Arimilli *et al.* (2000) *Immunological Rev. 177*:43-51).

The instant inventors recognized that chemokines play an intimate role in these varied diseases, and, as described in the application, provide a large repertoire of molecules that interact with an array of receptors. It is the instant inventors who have identified chemokine receptors as ideal targets for delivery of therapeutics, such as toxins. None of the cited art teaches or suggest selection of this set of receptors as targets for delivery of therapeutics.

Having provided the mode of intervention, the use of chemokines as targeting agents as described herein, one of skill in the art will recognize by virtue of knowledge in the art and the disclosure in the application, that the method provides a means for treatment of any disease in which in inappropriate triggering, disregulation or over-activation of the immune response is involved.

The instant applicant is **not** claiming the concept that these diseases are linked by an underlying pathology, such concept is recognized by those of skill in the art, but **is** providing a new avenue of treatment that exploits the common

underlying pathology. In contrast, as discussed below, prior and other targeting agents (such as those in Table 3) target the diseased cells or tissues, which is a very different treatment modality.

Differences between the teachings of the cited references and claimed subject matter

Ogata *et al.*

Ogata *et al.* teaches the construction of a recombinant chimeric toxin containing the non-chemokine cytokine, IL-4 linked to the cell binding domain of *Pseudomonas* exotoxin as a reagent for studying the function of the IL-4/Il-4 receptor system. Ogata *et al.* does not teach the use of its conjugate for treatment of any disorders nor suggest substitution of the non-chemokine cytokine with a chemokine.

IL-4 and Il-2 are not a chemokines, but area haematopoietins that target class I cytokine receptors, not chemokine receptors, which are a different class of receptors (see Collard *et al.*, cited by the Examiner in co-pending U.S. Patent No. 09/453,851 in the Information Disclosure Statement, mailed July 10, 2001 in this application). As stated in Collard *et al.* chemokine receptors are members of the Rhodopsin family.

Page 19, lines 24 to 26, of the description in the instant specification specifically provides that "these [targeting] agents do not include non-chemokine cytokines, such as IL-4...."

Volk *et al.*

Volk teaches that the chimeric protein IL-2-PE40 has been shown to have immunosuppressive efficacy in some models. As noted above, IL-2 is not a chemokine targeting agent. Furthermore, Volk *et al.* teaches that its IL-2 toxin conjugate has apparently dichotomous effects on humoral and responses. Volk *et al.* appears to resolve this apparent dichotomy by showing that Il-2-PE4- can induce signal transduction in activated T cells before exerting its cytotoxic effect. Since the humoral response requires T cell help for only a limited period, the short-term stimulation of T helper cells by Il-2-PE40 may be sufficient to

mediate a B cell response. As a result, the conjugates of Volk *et al.* teaches that its conjugates are not very useful as immunosuppressive agents, since they also mediate a B cell response.

At page 2504, first full paragraph, of the cited reference, Volk *et al.* concludes that:

> Addition of a toxic moiety to IL-2R targeting therapy, like IL-2-PE40, seems to improve the immunosuppressive efficacy on the cell-mediated immune response; but does not solve the problem of an undesired humoral immune response. This conclusion could not be predicted from *in vitro* cytotoxicity experiments. Therefore, the application of IL-2-PE40 immunotherapy has limitations: 1) The production of undesired pathogenically relevant Abs cannot be prevented..., and 2) the formation of Abs to the chimera, particularly to the toxin moiety, may interact with the sometimes required long-term or repeated administration of IL-2-PE40. [emphasis added]

Consequently, Volk *et al.* teaches that its conjugates are not useful for their intended purpose as immunosuppressive agents.

Volk *et al.* neither teaches nor suggests substitution of a chemokine receptor targeting agent in its conjugate nor the conjugate of Ogata *et al.*. Further, as mentioned above, Volk *et al.* does not teach a method of treating inflammatory disorders. Specifically, Volk *et al.* teaches away from using the IL2-PE40 conjugate in IL-2-receptor targeting therapy and concludes that this conjugate has limitations that prevent such use. Thus, the cited references do not suggest or motivate the combination suggested in the Office Action or claimed in the present application.

In contrast, the instant application and DECLARATION of record evidence that the instant conjugates are effective not only as targeting agents and exert a cytotoxic effect on the targeted cells. The instant conjugates, when internalized by a cell bearing a chemokine receptor, are designed to alter metabolism or gene expression in the cell, regulate or alter protein synthesis in the cell, inhibit proliferation of the cell or kill the cell.

Applicant's alleged admission

Table 3, was provided in connection with the last response methods of treatment involving elimination of immune cells is known. The immune cells targeted by the agents listed in that table, however, are the diseased cells, such as in leukemias, and lymphomas, and hence, represent a different treatment modality from that claimed in the instant application. Table 3 does not teach or suggest that conjugates of chemokines and therapeutic agents, such as toxins, have been used for targeting to immune cells to alter the pathology of the immune response in diseases that share this underlying common pathology. Table 3 does not suggest substitution of a chemokine receptor targeting agent for the interleukins in the conjugates of Volk *et al.* or Ogata *et al.* The agents described in the Table, as do those of Volk *et al.* and Ogata *et al.*, target the actual diseased tissues, such as the solid tumors.

The portion of the table to which the Examiner refers cites Bexxar and Genimmune™. Bexxar is a radiolabeled (^{131}I) monoclonal antibody that is in trials for treatment of B-cell non-Hodgkin's lymphoma that is targeted directly to the cancerous B-cells (see, *e.g.*, http://www.lymphomainfo.net/therapy/immunotherapy/bexxar.html). Bexxar binds only to a protein present on B-cells, such as those in non-Hodgkins B-cell lymphoma. The radioactivity targets the cancerous B-cell and destroys it. Hence the knowledge of Bexxar provides no teaching or suggestion relevant to the instant claims.

Genimmune™ (see, *e.g.*, products at www.xoma.com) is a fusion of a humanized single-chain anti-CD5 antibody binding domain linked to the recombinant toxin rGelonin. This agent targets cells that express CD5 receptors, which are expressed on cells involved in autoimmune diseases and some immune cell cancers. Hence, neither ligand fusion protein is targeted to chemokine receptors or would suggest such target. Similarly, knowledge of Genimmune™ provides no teaching or suggestion relevant to the instant claims.

The table of information was provided to show that targeted cells, such as B-cells, can be eradicated. There is no admission in the Table that the data therein is prior art to the instant application. As stated in the response, some of the arguments were provided "not to establish enablement, but to demonstrate operativeness and to evidence confirmation of what is taught in the instant application and doubted by the Examiner." Notwithstanding the fact the products noted in the Table are not relevant to the patentability of the instantly claimed methods (or the products), the dates for the products noted in the Table are not necessarily prior to the effective filing date of this application. Extensive Information Disclosure Statements have been made of record in this application.

Applicant's alleged admission was provided to show examples of cell depleting therapeutics. Most of the agents in the table are monoclonal antibodies. The so-called ligand fusions are Bexxar and Genimmune™. Bexxar is an ^{131}I-labeled monoclonal antibody that binds to and depletes B-cells, and Genimmune™ is a fusion of an anti-CD52 single chain humanized antibody binding domain fused to a recombinant gelonin. CD52 is present on cells in certain immune cell tumors. The agents listed in the table are no more relevant to the instant claims than Ogata *et al.* singly or in combination with Volk *et al.*.

Each of the products in the table, however, are designed to target the disease-causing cells, not the underlying pathology of a disease. The table neither teaches nor suggests selection of chemokine receptor targeting agents (or portions thereof) for selective targeting to the panoply of cells involved in the underlying pathology of associated with inflammatory responses and secondary tissue damage associated with activation, proliferation and migration of immune effector cells by inhibiting activation, proliferation or migration of immune effector cells as claimed in the instant application.

The combination of teachings of the cited references does not result in any of the instantly claimed methods

Substitution of the conjugate of Ogata *et al.* in the method of Volk *et al.* in view of the products listed in the table does not result in the instantly claimed methods. The combination does not result in method that targets cells that express chemokine receptors. As discussed above, neither Ogata *et al.* nor Volk *et al.* nor Table 3, singly or in any combination thereof, teaches or suggests methods involving targeting chemokine receptors using a conjugate containing a chemokine receptor targeting agent, such as a chemokine. No reference teaches or suggests substituting a chemokine for the interleukin used in the conjugates of Volk *et al.* or Ogata *et al.* nor in the agents set forth in the Table. In fact, Volk *et al.* teaches that its conjugates are not useful for their intended purpose as immunosuppressive agents, and hence Volk *et al.* teaches away from such use.

None of the listed agents, nor the agents of Ogata *et al.* and/or Volk *et al.*, target chemokine receptors nor suggest an avenue of the therapeutic intervention that exploits the common underlying response (termed an underlying pathological response in the claims) as claimed in this application. Selection of this pathway for therapeutic intervention is not taught or suggested in the Table nor does it suggest selection of chemokines as targeting agents or methods for treatment of the pathology underlying a pathological immune response or secondary tissue damage.

Therefore, the combination of teachings of the cited references and the noted Table does not result in the instantly claimed methods (nor in the conjugates used in the methods). Furthermore, as noted previously, Volk *et al.* teaches away from the combination, since it teaches that its conjugates do not work very well. There is no teaching or suggestion in any reference to substitute chemokine targeting agents for the monoclonal antibodies or interleukins in the agents in Table or in Volk *et al.* or Ogata *et al.* There is no suggestion for a method of treatment of inflammatory responses and/or

secondary tissue damage. As discussed above, the agents in the Table and in the cited references are designed to target the diseased cells and tissues, not to inhibit activation, migration or proliferation of immune cells as a treatment modality.

The ordinarily skilled artisan would not have been motivated to do what applicant has done

As stated above, the prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. Stratoflex Inc. v Aeroquip Corp., 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 USPQ 1783 (Fed. Cir. 1992).

In this instance, no art of record nor the data in the Tables, teaches or suggests or provides any motivation for targeting to cells that express chemokine receptors as a means to inhibit migration, proliferation or activation of immune cells that underlie pathology associated with inflammatory responses and/or secondary tissue damage. The cited references teach agents that target tumor-specific receptors or IL-2 or IL-4 receptors. None of the cited references or the Table teaches or suggests a method for targeting cells that express chemokine receptors. Accordingly, none of the cited art, singly or in any combination thereof provides a motivation to do that which applicant has done.

For the combination of references to result in the instantly claimed methods requires the improper use of hindsight.

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

In this instance, as discussed above, the combination of teachings does not result in the instantly claimed methods that require targeting cells that express chemokine receptors. None of the cited art teaches, suggests or mentions anything regarding chemokines or chemokine receptors, or treatments that target such receptors. Accordingly, to have combined the cited references and the Table to result in the instantly claimed methods requires the use of the teachings of the instant application.

Therefore, the Examiner has failed to set forth a prima facie case of obviousness.

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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